Potential depressive central nervous system effects of brimonidine topical gel

Cristina Foschi, BS,[a] and Elizabeth Damstetter, MD[b]
Chicago, Illinois

INTRODUCTION

Brimonidine 0.33% topical gel is a Food and Drug Administration–approved treatment for rosacea that acts as an α_{2a}-adrenergic agonist on cutaneous vessels, resulting in vasoconstriction.[1] Within the central nervous system, stimulation of these receptors has the opposite effect, inhibiting adrenergic neurotransmission and resulting in central nervous system depression.[2] Although its clinical use is to act at the peripheral α_{2a}-adrenergic receptors, its highly lipophilic nature may allow it to act at inner central nervous system α_{2a}-receptors, resulting in depressive effects.[3] Although the package insert cautions against using brimonidine for patients with a history of depression, there has not been clear evidence explaining why. Here, we report a case of abrupt worsening of depression and anxiety while topical brimonidine 0.33% gel was used for rosacea.

CASE PRESENTATION

A 37-year-old white woman with a 3-year history of depression and anxiety presented to dermatology for rosacea. She was prescribed brimonidine 0.33% topical gel to use on her face for treatment in accordance with its Food and Drug Administration–approved indication (persistent/nontransient erythema of rosacea) and used the medication daily as directed.

One week after beginning the once-daily topical application, the patient reported feeling intense episodes of anxiety and depression. She experienced no other systemic symptoms during this time, and there were no medication changes, drug use, or stressful life events. The patient had been stable while receiving 50 mg of sertraline daily since 2016, with ongoing therapy every 2 weeks, and had never been hospitalized for her anxiety or depression. She immediately discontinued the medication as directed by her physician. Two weeks after discontinuing, she reported that her mood had stabilized and that the worsening anxiety and depression symptoms fully resolved. Given the sudden and intense change in her mood after initiation of topical brimonidine and the subsequent full resolution of her symptoms on discontinuation, the patient expressed concern about a potential adverse reaction. No further rechallenges were thought clinically appropriate or advised.

DISCUSSION

Although brimonidine 0.33% gel has been proven to be an effective treatment for rosacea by acting as peripheral α_{2a}-adrenergic agonist on cutaneous vessels, its ability to cross the blood-brain barrier and cause central nervous system depression at central receptors should also be considered.[3] Two cases were reported of patients experiencing deterioration of mental status, respiratory depression, and somnolence after using 10 g of brimonidine under occlusion of a large surgical wound that needed hemostasis.[4] Both patients had their mental status return to baseline 18 hours after application of brimonidine.[4] Although this seems to suggest the toxicity of central nervous system depression caused by stimulation of centrally acting α_{2a}-adrenergic receptors, there have been conflicting cases in the literature. Another study demonstrated the benefit of using 1 g of brimonidine 0.33% gel as a hemostatic agent in 10 patients who underwent nail surgical procedures.[5] Although these patients did not report any central nervous system depressive effects afterward, it implies that there is this risk in using brimonidine as a hemostatic agent in infants with underdeveloped blood-brain barriers.[5] In addition,

From Rush Medical College, Chicago[a]; and Department of Dermatology, Rush University Medical Center, Chicago.[b]

Funding sources: None.

Conflicts of interest: Dr Damstetter was a speaker for Galderma and received honoraria. Author Foschi has no conflicts of interest to declare.

Correspondence to: Cristina Foschi, BS, Rush Medical College, 600 S Paulina St, Chicago, IL 60607. E-mail: cristina_foschi@rush.edu.

JAAD Case Reports 2020;6:979-80.
2352-5126

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https://doi.org/10.1016/j.jdcr.2020.07.037

the amount of brimonidine used for hemostasis and the surface area of the lesions varied greatly between these 2 studies, suggesting that further investigation is needed to fully understand this potential adverse effect.

Central α_{2a}-adrenergic receptors have also been found in higher densities in the brain tissue of individuals who commit suicide and had a major depressive disorder.[6] Many studies have found a higher functional sensitivity of α_{2a}-receptors within the prefrontal cortex in individuals with depression, and that long-term administration of antidepressants results in a reduced functional activity of these receptors.[6] In particular, the density and affinity of α_{2a}-adrenoceptors are increased in the prefrontal cortex, amygdala, hippocampus, and the cerebellum of depressed patients.[7] Because clinical depression has been proven to be a common comorbidity in patients with rosacea, this finding is significant in deciding whether to use brimonidine gel for rosacea treatment.[8]

We present this case of an abrupt worsening of clinical depression and anxiety after initiation of brimonidine that may be explained by its effects on central α_{2a}-receptors. It is possible that transcutaneous absorption allowed brimonidine to enter the bloodstream, cross the blood-brain barrier, and intensify feelings of anxiety and depression. Because the patient had received a diagnosis of clinical depression and anxiety before drug administration, as the literature has shown, she may have an increased density of α_{2a}-adrenergic receptors within these brain regions for the drug to act on. We believe further research must be conducted to continue to understand the potential psychiatric effects of brimonidine in patients with clinical anxiety and depression.

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